A longitudinal study of the effects of tobacco and cannabis exposure on lung function in young adults

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Submitted 30 November 2001;
initial review completed 7 January 2002;
final version accepted 19 February 2002

ABSTRACT

Aim To assess the possible effects of tobacco and cannabis smoking on lung function in young adults between the ages of 18 and 26.

Setting and participants A group of over 900 young adults derived from a birth cohort of 1037 subjects born in Dunedin, New Zealand in 1972/73 were studied at age 18, 21 and 26 years.

Measurements Cannabis and tobacco smoking were documented at each age using a standardized interview. Lung function, as measured by the forced expiratory volume in one second/vital capacity (FEV_1/VC) ratio, was obtained by simple spirometry. A fixed effects regression model was used to analyse the data to take account of confounding factors.

Findings When the sample was stratified for cumulative use, there was evidence of a linear relationship between cannabis use and FEV_1/VC ($P < 0.05$). In the absence of adjusting for other variables, increasing cannabis use over time was associated with a decline in FEV_1/VC with time; the mean FEV_1/VC among subjects using cannabis on 900 or more occasions was 7.2%, 2.6% and 5.0% less than non-users at ages 18, 21 and 26, respectively. After controlling for potential confounding factors (age, tobacco smoking and weight) the negative effect of cumulative cannabis use on mean FEV_1/VC was only marginally significant ($P < 0.09$). Age ($P < 0.001$), cigarette smoking ($P < 0.05$) and weight ($P < 0.001$) were all significant predictors of FEV_1/VC. Cannabis use and daily cigarette smoking acted additively to influence FEV_1/VC.

Conclusions Longitudinal observations over 8 years in young adults revealed a dose-dependent relationship between cumulative cannabis consumption and decline in FEV_1/VC. However, when confounders were accounted for the effect was reduced and was only marginally significant, but given the limited time frame over which observations were made, the trend suggests that continued cannabis smoking has the potential to result in clinically important impairment of lung function.

KEYWORDS Cannabis, epidemiology, lung function, smoking, tobacco.

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INTRODUCTION

In the last three decades, cannabis use has increased significantly in most developed societies (Hall *et al.* 1999). In New Zealand, cannabis use by young people is now commonplace: up to two-thirds of young people will have used cannabis on at least one occasion by age 21, with nearly 10% meeting criteria for cannabis dependence (Poulton *et al.* 1997; Fergusson & Horwood 2000). This has led to widespread concern and debate about its health effects (Hall & Solowij 1998), including adverse effects on respiratory function. There is evidence to suggest that smoking cannabis results in acute airway inflammation as well as important histological changes in the airway mucosa (Fligiel *et al.* 1997; Roth *et al.* 1998), and that with more chronic exposure this may give rise to symptoms of cough and abnormal sputum production, as well as changes in lung function consistent with airflow limitation (Tashkin *et al.* 1980, 1987; Bloom *et al.* 1987; Sherrill *et al.* 1991; Taylor *et al.* 2000).

One of the threats to the validity of these data is the effect of third or confounding factors. This is particularly so if the association between cannabis use and respiratory function reflects the confounding effect of a factor which is not only strongly associated with cannabis use, but which itself has an adverse effect on respiratory function. Cigarette smoking is the most important example: the majority of subjects who use cannabis also smoke cigarettes (Taylor *et al.* 2000), and cigarette smoking has a detrimental effect on lung function (US Surgeon General 1984). This is all the more problematic because although the pathological effects of inhaling both tobacco and cannabis smoke appear to be similar (Fligiel *et al.* 1997; Roth *et al.* 1998), quantifying total exposure to cannabis is much more difficult. Thus associations between cannabis use and respiratory function need to be controlled for confounding factors.

Further difficulties arise in dealing with non-observed sources of confounding. It is often believed that in the analysis of epidemiological data, it is possible to control only for those factors which are observed, making the analyses vulnerable to non-observed confounding factors (Fergusson & Horwood 2000; Judge *et al.* 1980). We have used a fixed effects regression model to investigate linkages between cumulative cannabis use and respiratory function in young adults using data from a longitudinal birth cohort study of nearly 1000 New Zealand young people studied at ages 18, 21 and 26. Subject to some assumptions, this model makes it possible to control all observed and non-observed fixed sources of confounding, i.e. whose effects on outcome do not vary with time (Fergusson & Horwood 2000). The model does not control fully for all sources of time-dynamic confounding, i.e. variables that vary with time or have time-specific effects on outcomes. Only the effects of *observed* time-dynamic confounders can be controlled. In the present analysis we have controlled for time-dynamic confounding by cigarette smoking, height and weight.

The aims of the present paper were:

1 To document the association between the cumulative use of cannabis between the ages of 18 and 26 on lung function (forced expiratory volume in one second/vital capacity ratio; FEV_1/VC).

2 To examine the combined and separate effects of cigarette smoking and cannabis use on lung function.

3 To apply the fixed effects model to take account of all fixed sources of confounding and the effects of time-dynamic confounders.

METHODS

The study sample consisted of members of the Dunedin Multidisciplinary Health and Development Study (Silva & Stanton 1996), a birth cohort comprising 1037 children born in Dunedin, New Zealand, in 1972–73. Study members have been assessed longitudinally at ages 3, 5, 7, 9, 11, 13, 15, 18, 21 and 26 years with respect to a diverse array of medical, psychological and sociological measures. Of those still living, 96.7%, 97.2% and 96.2% were followed-up at ages 18, 21 and 26, respectively, although not all those followed-up completed every assessment.

The following end-points were evaluated in the present study.

Cannabis use

At ages 18, 21 and 26, the same questionnaire was administered to study members to document the number of occasions on which they used cannabis in the preceding 12 months. To develop an index of cumulative exposure, a time-dynamic variable was constructed by summing the frequency of cannabis exposure up to ages 18, 21 and 26. Since study members were not assessed every year between age 18 and 26, this measure gives only a proxy for the true but non-observed cumulative levels of cannabis exposure.

Respiratory function

Spirometry was performed at ages 18 and 26 using a computerized spirometer and body plethysmograph, and at age 21 using a water-sealed Godart spirometer (Sears *et al.* 1986). The same three trained technicians were responsible for pulmonary function measurements on each occasions at only one centre. The spirometers were calibrated regularly with a 3-litre syringe. Measurements

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of slow vital capacity were repeated to obtain at least three satisfactory and repeatable values (to within 5%), followed by full forced expiratory maneuvers to record FEV_1, again on at least three occasions to obtain reproducible data. The FEV_1/VC ratio was used as the primary lung function measurement because it is the most sensitive measure for assessing the possible development of airways remodelling in a large population (Rasmussen *et al.* 2002).

Time-dynamic covariates

To control for possible confounding by time dynamic factors which correlated with both cannabis use and respiratory function, the following data obtained at ages 18, 21 and 26, were used in the analysis.

1 *Cigarette smoking.* Study members were asked if they had smoked tobacco daily for at least a month of the previous year. Those who had done so were asked how many cigarettes per day they typically smoked.

2 *Height and weight.* Height was measured to the nearest millimetre using a portable Harpenden Stadiometer. Weight was recorded to the nearest 0.1 kg using calibrated scales (Tanita, model no.1609 N).

Sample size

Data on cannabis use and respiratory function at 18, 21 and 26 were available for a maximum of 930 study members (89.7% of original cohort at entry). Because not all study members completed the cannabis and respiratory assessments at each age, the number of observations available for analysis at any one time point ranged from 859 to 930.

Statistical analysis

A fixed effects regression model was used to analyse the data (Stata Statistical Software V. 7, Stata Corporation, College Station, TX, USA). These models explore possible relationships between an exposure variable *X* and a continuous outcome *Y* which are both observed at repeated times. A fuller description of fixed effects models is given by Fergusson & Horwood (2000) and Judge *et al.* (1980).

Briefly, let *Xit* denote the score of the *i*th subject at time *t* and *Yit* the corresponding score on *Y* for the *i*th subject at time *t*. Assume that *Yit* and *Xit* are linked by the model in equation 1:

$$Yit = B0 + B1Xit + Ui + Eit, \qquad \text{(eqn 1)}$$

where *Ui* represents non-observed systematic factors that influence the outcome *Y* for subject i and *Eit* is a random error term. The non-observed variable *Ui* represents all fixed (i.e. time invariant) factors, aside from *Xit*, that influence the score *Yit*, and thus represents all potential fixed sources of confounding that could influence the relationship between *Xit* and *Yit* (i.e. stable characteristics of subjects and their life-styles that may influence lung function). Normally *Ui* would need to be observed to estimate the causal effect *B1* of *Xit* on *Yit* in equation 1. However, it is possible to account for *Ui*. First, sum equation 1 over the time periods *t* ($t = 1 \ldots n$) and divide both sides by *n*. This operation yields equation 2:

$$yi = B0 + B1xi + Ui + ei, \qquad \text{(eqn 2)}$$

where *yi* is the mean value of *Yit* over the *n* time periods, *xi* is the corresponding mean value of *Xit* and *ei* is the mean value of the disturbance *Eit*.

Next, subtract equation 2 from equation 1 to give equation 3:

$$(Yit - yi) = B1(Xit - xi) + (Eit - ei). \qquad \text{(eqn 3)}$$

Equation 3 provides a means of estimating the parameter of interest B1 in a way that takes into account the non-observed fixed sources of confounding represented by the variable *Ui*. Further, the fixed effects model in equation 3 can be extended to include observed time-dynamic variables:

$$(Yit - yi) = B1(Xit - xi) + \Sigma Bj(Zijt - zij) + (Eit - ei), \qquad \text{(eqn 4)}$$

where the variables *Zijt* are covariate measures that may vary with time (e.g. body weight or tobacco smoking) and *zij* is the mean of the *j*th covariate *Zijt* over the *n* time periods. The effect of cannabis use on FEV_1/VC was estimated using the fixed effects model expressed in equation 4, above.

RESULTS

Cumulative cannabis use and FEV_1/VC

The relationship between cumulative use of cannabis and the FEV_1/VC ratio at ages 18, 21, 26 is shown in Table 1. The cannabis measure is divided into seven class intervals ranging from non-use to use on more than 900 occasions. For each age (18, 21 and 26), the relationship between cannabis use and FEV_1/VC was tested for significance using a one-way analysis of variance, and evidence of a significant linear trend was obtained ($P < 0.05$). At each age, increasing cannabis use was associated with a decline in FEV_1/VC. Subjects using cannabis on 900 or more occasions had mean FEV_1/VC values that were 7.2%, 2.6% and 5.0% less than non-users at ages 18, 21 and 26, respectively (see Table 1).

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Table 1 Association between cumulative cannabis use (with or without concomitant tobacco) and mean FEV_1/VC at ages 18, 21, 26 years. The number of observations is in brackets.

	Accumulative use of cannabis[a]							
Age	*0*	*1–10*	*11–100*	*101–300*	*301–600*	*601–900*	*901+*	P[b]
18	87.7 (456)	87.3 (252)	86.2 (96)	84.0 (33)	86.5 (15)	75.1 (3)	80.5 (4)	<0.001
21	84.7 (364)	85.2 (258)	84.5 (164)	84.3 (81)	80.4 (35)	85.7 (17)	82.1 (8)	<0.05
26	82.4 (284)	83.1 (241)	82.3 (217)	82.4 (80)	80.5 (45)	82.0 (21)	77.4 (42)	<0.001

[a] Hall *et al.* (1999): the cumulative use of cannabis is a time-dynamic variable whose distribution varies with age. The numbers in the table show these age-related variations. For example, at age 18, 456 subjects had never used cannabis, whereas by age 26, this number had fallen to 284.
[b] Poulton *et al.* (1997): one-way analysis of variance for linear trend.

Adjustment for fixed effects and time-dynamic covariates

To adjust the results contained in Table 1 for non-observed fixed sources of confounding and time dynamic confounding, the data were analysed using a regression model in which the cumulative use of cannabis was used as a predictor of FEV_1/VC after adjustment for fixed effects and a series of time-dynamic factors assessed at ages 18, 21 and 26. The time-dynamic factors were: age; cigarette smoking (divided into six class intervals ranging from non-smokers to those smoking 20+ cigarettes per day); height; and weight. The results are shown in Table 2. After controlling for fixed effects and observed time-dynamic factors, cumulative cannabis use had only a marginally significant effect on mean FEV_1/VC ($P = 0.082$). Separate identical analyses were undertaken using FEV_1 as the dependent variable: this resulted in a strengthening of the observed associations ($P = 0.016$). Age ($P < 0.001$), cigarette smoking ($P < 0.05$) and weight ($P < 0.001$) were all significant predictors of FEV_1/VC.

Table 2 Fitted fixed effects model including time dynamic covariates using FEV_1/VC as the dependent variable.

Predictor	β[a]	*SE*	P[b]
Cannabis use	–0.221	0.127	0.082
Cigarette smoking	–0.179	0.087	0.041
Age	–0.489	0.029	0.001
Height (cm)	–0.100	0.081	>0.20
Weight (kg)	–0.084	0.015	0.001

[a] Unstandardized coefficient of regression; [b] *t*-test.

Combined effects of cigarette smoking and cumulative cannabis use

Estimates of the effects of cumulative cannabis use on decrement in FEV_1/VC relative to non-use are shown in Table 3. The results show that those who had used cannabis on > 900 occasions had mean FEV_1/VC values that were 1.33% lower than non-users. As shown in Table 2, cigarette smoking was a significant predictor of FEV_1/VC ($P < 0.05$). However, there was no significant interaction between cannabis use and cigarette smoking ($\beta = 0.02$; $t = 0.53$; $P = 0.59$). This suggests that cumulative cannabis use and daily cigarette smoking act additively to influence FEV_1/VC. Estimates of the decrement of FEV_1/VC for combinations of both cigarette consumption and cannabis use are shown in Table 3. Those who used cannabis on more than 900 occasions and who smoked 20+ cigarettes per day had mean FEV_1/VC values that were 2.2% lower than those who smoked neither cannabis nor tobacco.

DISCUSSION

In this report, we have examined the relationship between cumulative cannabis use in a birth cohort of nearly 1000 young adults studied between ages 18 and 26, and a single measure of respiratory function, the FEV_1/VC ratio. Cannabis exposure at ages 21 and 26 among study members was approximately 50% for occasional use, and nearly 10% were cannabis-dependent at each age (Taylor *et al.* 2000; Poulton *et al.* 2001). [Cannabis dependence was based on DSM-III-R criteria, and implied daily or almost daily cannabis exposure in association with positive behavioral features relating to the time spent using, obtaining or recovering from the effects of cannabis use (Poulton *et al.* 1997).] Although based on self-reported use, the accuracy of data obtained from our study members has been assessed repeatedly (Silva & Stanton 1996). If any errors did occur regarding the extent of cannabis/tobacco exposure, then these would tend to have attenuated the association which we have reported (Stanton *et al.* 1996).

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Table 3 The estimated combined (additive) effects (standard errors) of cumulative cannabis use and daily cigarette smoking on mean FEV_1/VC. The bold figures show the estimated effects of cannabis use alone.

	Cumulative cannabis use (total number of exposures)						
Cigarettes per day	*0*	*1–10*	*11–100*	*101–300*	*301–600*	*601–900*	*901+*
0		**–0.221**	**–0.442**	**–0.664**	**–0.885**	**–1.105**	**–1.327**
	0	**(0.127)**	**(0.254)**	**(0.382)**	**(0.509)**	**(0.636)**	**(0.763)**
1–4	–0.179	–0.400	–0.621	–0.842	–1.064	–1.285	–1.506
	(0.087)	(0.144)	(0.258)	(0.380)	(0.505)	(0.630)	(0.757)
5–9	–0.358	–0.579	–0.800	–1.021	–1.242	–1.464	–1.685
	(0.175)	(0.202)	(0.289)	(0.398)	(0.516)	(0.637)	(0.760)
10–14	–0.536	–0.758	–0.979	–1.200	–1.421	–1.642	–1.864
	(0.262)	(0.275)	(0.340)	(0.433)	(0.540)	(0.655)	(0.773)
15–19	–0.715	–0.936	–1.158	–1.379	–1.600	–1.821	–2.042
	(0.349)	(0.355)	(0.404)	(0.482)	(0.577)	(0.684)	(0.796)
20+	–0.894	–1.115	–1.336	–1.558	–1.779	–2.000	–2.221
	(0.436)	(0.438)	(0.475)	(0.540)	(0.625)	(0.722)	(0.827)

Previously, we have examined the respiratory effects of cannabis use at a single point in time (i.e. age 21) in the same cohort (Taylor *et al*. 2000). However, the present study has a number of advantages including: (1) *longitudinal* assessment of lung function over an 8-year period; (2) the use of a general population cohort in which there have been low rates of sample attrition; (3) repeated documentation of cannabis use via standardized questionnaire methods over a time interval when cannabis use is likely to be most prevalent; and (4) repeated assessment of potentially confounding factors including cigarette smoking, height and weight. In addition, the longitudinal nature of the study has also made it possible to use the comparatively powerful technique of fixed effects regression to control for both observed and non-observed fixed sources of confounding. The disadvantage of our study is that between the ages of 18 and 26 lung growth may not yet be completed in some individuals, and thus any changes attributable to cannabis or tobacco smoking are occurring at a time when age-related decline in lung function is not yet fully established.

In the present study, young people who had smoked cannabis on 900+ occasions had mean FEV_1/VC ratios that were 2.6% to 7.2% lower than non-smokers (Table 1). We also undertook analyses using FEV_1 as the dependent variable, the results of which were statistically more significant than for FEV_1/VC. However, we have chosen to focus on the influence of cannabis/tobacco exposure on the FEV_1/VC ratio, given that this is a more sensitive and clinically meaningful test for changes in airway structure and function. Overall, our results suggest that heavy cannabis users are an at-risk group for the development of impaired lung function. However, the observed correlation between cumulative cannabis use and FEV_1/VC does not necessarily establish a causal link between the two. A major threat to the validity of a potentially causal inference comes from the possibility that third or confounding variables are responsible. These may be: (a) associated with cannabis use; and/or (b) associated with changes in respiratory function. Cigarette smoking is clearly an example of such a factor. In this study, we have used fixed effects regression analysis to control for both non-observed fixed sources of confounding as well as observed time-dynamic covariates, including cigarette smoking. The results of this analysis showed that, after allowing for confounding factors, the relationship between cannabis use and FEV_1/VC approached but did not reach conventional levels of statistical significance ($P = 0.082$). Cannabis users of more than 900 occasions had a mean FEV_1/VC which was 1.33% lower than non-users of cannabis (after controlling for confounders).

Our study showed evidence that after controlling for other confounding factors, the small but detectable effect on FEV_1/VC for both tobacco and cannabis use persisted. Those most at risk of impaired FEV_1/VC were those who had smoked cannabis on at least 900 occasions and who were also smoking 20+ cigarettes per day. Although numbers were small, members of this group had an estimated mean FEV_1/VC which was 2.2% arithmetically lower than those who smoked neither tobacco nor cannabis (Table 3). While it would be tempting to use the results of the present study to compare the relative effects of cannabis and tobacco smoking on lung function, we believe that because of the approximate nature of the measurement of cannabis use, such comparisons are potentially misleading.

Our findings must be considered alongside the results of previous studies in this area (Bloom *et al*. 1987; Sherrill *et al*. 1991; Tashkin *et al*. 1987, 1997). In the

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study by Tashkin *et al.* (1997), healthy volunteers aged 33 ± 6 years with a mean consumption of 3.5 joints per day consumed over 4.9 ± 2.0 years, were studied. No significant adverse trend in lung function was identified among cannabis users, in contrast to a significant decline in FEV_1 among tobacco cigarette smokers. In contrast, Sherrill *et al.* (1991) reported a significant reduction in FEV_1 of 142 ml over 6 years among ex-non-tobacco smokers drawn from a wider population of 856 subjects, when comparisons were made against non-smokers. This contrasted with a surprising increase in FEV_1 among *current* non-tobacco smokers when a similar comparison was made. For FEV_1/FVC ratio, a reduction of 1.9% was observed, a figure which is slightly less than our own finding but which was statistically significant. In another study by Bloom *et al.* (1987), there was a reduction in FEV_1/FVC for males (but not females) when comparisons were made between never-smokers and non-tobacco cigarette users (from 98.4% *of predicted values* among never-smokers to 90.0% among 'non-tobacco cigarette' users). Taken together, the impact of cannabis smoking *alone* on spirometric values, appears to be somewhat less than for cigarette smoking. However, the populations studied differ as to selection criteria and age, and in the longitudinal studies the duration of observation for all of them is arguably too short (maximum 8 years) for a definitive conclusion to be reached.

The results of the present analysis suggest that cannabis use and daily tobacco smoking combine additively to influence in their effects on lung function. Although the magnitude of the changes in lung function associated with cannabis exposure may not be clinically significant, the findings suggest that if cannabis smoking were continued over a prolonged period along with tobacco use, this may potentially lead to important lung pathology in later years. It is likely that similar pathological changes would occur in the airways and lungs with combined use of tobacco and cannabis as occur with tobacco alone. Evidence to support this view has been obtained from histopathological studies (Fligiel *et al.* 1997; Roth *et al.* 1998). Scores for vascular hyperplasia, submucosal oedema and goblet cell hyperplasia, all of which predispose to eventual airways obstruction in tobacco smokers, were found to be equally prevalent in young cannabis smokers (Roth *et al.* 1998).

In the controversy surrounding the health effects of cannabis and its legal status, opinions have polarized between those who consider cannabis to be relatively free of harmful effects and those who consider it to be a major hazard. Our study adds weight to the view that the effects of smoking cannabis are not negligible particularly in heavy users, even though the magnitude of the negative effect on lung function is small in early adult life. The burden of morbidity associated with tobacco smoking is well established, occurring over a time course of 30–40 years often in a subset of exposed individuals (Murin & Silvestri 2000). A similar pattern may eventually emerge among those whose exposure to cannabis is equally prolonged.

ACKNOWLEDGEMENTS

This research was supported partially by a grant from the National Institute of Mental Health (MH-49414). The Dunedin Multidisciplinary Health and Development Study is supported by the Health Research Council of New Zealand. The authors wish to thanks the study members for their continued support.

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